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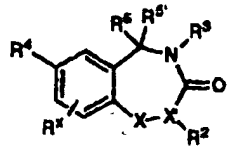
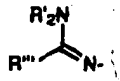


(I)



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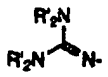

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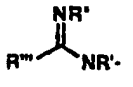

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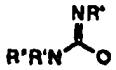

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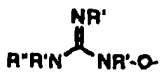

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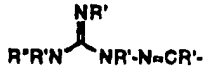

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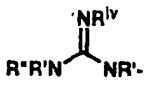

(j)

or 

(k)

(57) Abstract

Integrin receptor antagonists of formula (I) are disclosed, wherein: X-X' is NR^1-CH, $NC(O)R^3$-CH, N=C, CR^1=C, CHR^1-CH, O-CH or S-CH; R^1 is H, C_{1-6}alkyl, C_{3-7}cycloalkyl-C_{0-6}alkyl or ArC_{0-6}alkyl; R^2 is $(CH_2)_nCO_2R$; R^3 is H, C_{1-6}alkyl, Ar-C_{0-6}alkyl, Het-C_{0-6}alkyl, or C_{3-6}cycloalkyl-C_{0-6}alkyl; R^4 is Y-U; R^5 and $R^{5'}$ are R' or together are =O; R is H, C_{1-6}alkyl, benzyl or a carboxy protecting group; U is $-NR^1NR^1C(O)$, =N-N=CH or $-R^1NN$=CH; Y is W-$(CR'_2)_q$-Z-$(CR'R')_r$-; W is R'R'''N-, R'R''NR'N-, R'R''NR'NCO-, $R'_2NR'NC(=NR')$-, R'ONR'C(=NR')-, OH, (a), (b), (c), (d), (e), (f), (g), (h), (i), (j) or (k); R' is H, C_{1-6}alkyl, C_{3-7}-cycloalkyl-C_{0-4}alkyl or Ar-C_{0-4}alkyl; R'' is R', -COR', CO_2C_{1-6}alkyl or CO_2C_{0-4}alkyl-Ar; R''' is R', $-CF_3$, -SR', or -OR'; R^{iv} is R', COR', CN, NO_2, SO_2R', CO_2C_{1-6}alkyl or CO_2C_{0-4}alkyl-Ar; Z is $(CH_2)_t$, Het, Ar or C_{3-7}cycloalkyl; R^x is H, C_{1-4}alkyl, OR^1, SR^1, C_{1-4}alkyl, C_{1-4}alkylsulfonyl, C_{1-4}alkylsulfoxyl, -CN, $N(R^1)_2$, $CH_2N(R^1)_2$, $-NO_2$, $-CF_3$, $-CO_2R^3$, $-CON(R^1)_2$, $-COR^1$, $-NR^1C(O)R^1$, OH, F, Cl, Br, I or $CF_3S(O)_r$-; Q is NR^1, S or O; and pharmaceutically acceptable salts thereof.

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TITLE

Integrin Receptor Antagonists

FIELD OF THE INVENTION

This invention relates to pharmaceutically active compounds which inhibit integrin receptors and are useful for the treatment of pathological conditions in which integrin receptors, such as the fibrinogen and vitronectin receptors play a role.

BACKGROUND OF THE INVENTION

Integrins are a class of proteins which mediate adhesive events, such as adhesion of platelets to vessel walls and to one another. Platelet aggregation is believed to be mediated primarily through the fibrinogen receptor, or GPIIb-IIIa receptor complex, is an integrin found on platelets. It has been found that frequently the natural ligands of integrin receptors are proteins which contain an Arg-Gly-Asp sequence. Von Willebrand factor and fibrinogen, which are considered to be natural ligands for the GPIIb-IIIa receptor, possess an Arg-Gly-Asp (RGD in single letter amino acid code) sequence in their primary structure. Functionally, these proteins are able to bind and crosslink GPIIb-IIIa receptors on adjacent platelets and thereby effect aggregation of platelets.

Fibronectin, vitronectin and thrombospondin are RGD-containing proteins which have also been demonstrated to bind to GPIIb-IIIa. Fibronectin is found in plasma and as a structural protein in the intracellular matrix. Binding between the structural proteins and GPIIb-IIIa may function to cause platelets to adhere to damaged vessel walls. Inappropriate aggregation of platelets can lead to pathology, such as stroke, myocardial infarction, transient ischemia attacks, and related cardiovascular diseases.

Vitronectin is also found in the bone matrix. Mammalian bone is constantly undergoing a dynamic process referred to as bone remodeling, which is a dynamic process of bone resorption and bone formation. These processes are mediated by specialized cell types: bone formation is the result of the deposition of mineralized bone by osteoblast cells, and bone resorption is the result of the dissolution of bone matrix by osteoclast cells. Many bone diseases are brought about by an imbalance of bone formation relative to bone resorption. For instance, diseases such as osteoporosis are characterized by a net loss of bone matrix. Thus, agents which inhibit bone resorption are useful for the treatment of such diseases.

An activated osteoclast resorbs bone by attaching to the bone matrix, and secreting proteolytic enzymes, organic acids and protons into the sealed compartment formed between its cell membrane and the bone matrix. The acidic environment and proteolytic enzymes effect the dissolution of bone in the sealed compartment to create pits, or lacuna, in the bone surface, which are apparent when the osteoclast detaches from the bone.

Recent studies have indicated that the attachment of osteoclasts to the bone matrix is mediated through cell surface adhesion receptors which resemble the vitronectin receptor. For instance, Davies, *et al.*, *J. Cell Biol.* **1989**, *109*, 1817, disclose that the osteoclast functional antigen, which is implicated in the regulation of bone resorption, is biochemically related to the vitronectin receptor. The vitronectin receptor, or the $\alpha_v\beta_3$ integrin, is known to bind to bone matrix proteins, such as osteopontin, bone sialoprotein and thrombospondin, which contain the tri-peptide RGD motif. Thus, Horton, *et al.*, *Exp. Cell Res.* **1991**, *195*, 368, disclose that RGD-containing peptides and an anti-vitronectin receptor antibody (23C6) inhibit dentine resorption and cell spreading by osteoclasts. In addition, Sato, *et al.*, *J. Cell Biol.* **1990**, *111*, 1713 disclose that echistatin, a snake venom peptide which contains the RGD sequence, is a potent inhibitor of bone resorption in tissue culture, and inhibits attachment of osteoclasts to bone. Fisher, *et al.*, *Endocrinology* **1993**, *132*, 1411, has further shown that echistatin inhibits bone resorption *in vivo* in the rat. EP 528 587 and EP 528 586 report substituted phenyl derivatives which inhibit osteoclast mediated bone resorption.

Bondinell, *et al.*, in WO 93/00095 (PCT/US92/05463), WO 94/14776 PCT/US93/12436 and WO 95/18619 (PCT/US95/00248), disclose that certain compounds which have a substituted 6-7 bicyclic ring system are useful for inhibiting the fibrinogen receptor. Other compounds which have a 6-7 bicyclic ring system and inhibit the fibrinogen receptor are disclosed by Blackburn *et al.* in WO 93/08174 (PCT/US92/08788). Cousins, *et al.*, in WO 96/00574 (PCT/US95/08146), disclose benzazepine and benzodiazepine compounds which are inhibitors of the vitronectin

receptor. There is a continued need for new integrin receptor antagonists to treat diseases mediated by these receptors.

SUMMARY OF THE INVENTION

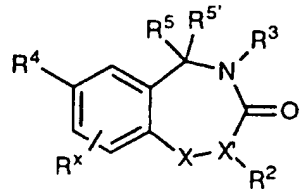
This invention comprises compounds of the formula (I) as described hereinafter, which have pharmacological activity for the inhibition of integrin receptors.

This invention is also a pharmaceutical composition comprising a compound according to formula (I) and a pharmaceutically acceptable carrier.

This invention is also a method for treating diseases which are mediated by ligands which bind to the vitronectin or fibrinogen receptor. In a particular aspect, the compounds of this invention are useful for treating osteoporosis and platelet aggregation.

DETAILED DESCRIPTION

This invention comprises compounds of formula (I):



(I)

wherein

X-X' is NR^1-CH, NC(O)R^3-CH, N=C, CR^1=C, CHR^1-CH, O-CH or S-CH;

R^1 is H, C_{1-6} alkyl , C_{3-7}cycloalkyl-C_{0-6}alkyl or ArC_{0-6}alkyl;

R^2 is $(CH_2)_nCO_2R$;

R^3 is H, C_{1-6}alkyl, Ar-C_{0-6}alkyl, Het-C_{0-6}alkyl, or C_{3-6}cycloalkyl-C_{0-6}alkyl;

R^4 is Y-U;

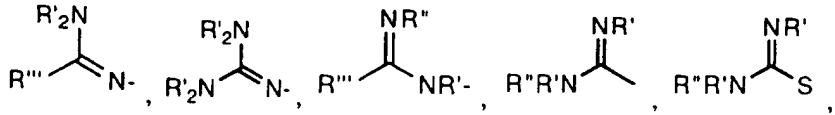
R^5 and $R^{5'}$ are R' or together are =O;

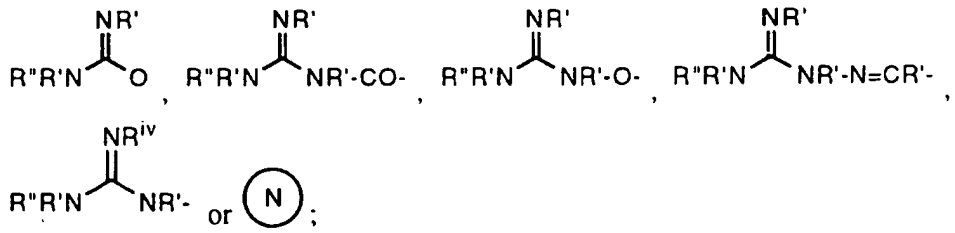
R is H, C_{1-6}alkyl, benzyl or a carboxy protecting group;

U is -$NR^1NR^1C(O)$, =N-N=CH or -R^1NN=CH;

Y is W-$(CR'_2)_q$-Z-$(CR'R')_r$-;

W is R'R'''N-, R'R''NR'N-, R'R''NR'NCO-, R'_2NR'NC(=NR')-, R'ONR'C(=NR')-, OH,





R' is H, C_{1-6}alkyl, C_{3-7}cycloalkyl-C_{0-4}alkyl or Ar-C_{0-4}alkyl;

R" is R', -COR', CO_2C_{1-6}alkyl or CO_2C_{0-4}alkyl-Ar;

R"' is R', $-CF_3$, -SR', or -OR';

R^{iv} is R', COR', CN, NO_2, SO_2R', CO_2C_{1-6}alkyl or CO_2C_{0-4}alkyl-Ar;

Z is $(CH_2)_t$, Het, Ar or C_{3-7}cycloalkyl;

R^x is H, C_{1-4}alkyl, OR^1, SR^1, C_{1-4}alkyl, C_{1-4}alkylsulfonyl, C_{1-4}alkylsulfoxyl, -CN, $N(R^1)_2$, $CH_2N(R^1)_2$, $-NO_2$, $-CF_3$, $-CO_2R^3$, $-CON(R^1)_2$, $-COR^1$, $-NR^1C(O)R^1$, OH, F, Cl, Br, I, or $CF_3S(O)_r$-;

Q is NR^1, S or O;

n is 0, 1 or 2;

q is 0 to 3;

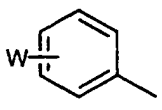
r is 0 to 2;

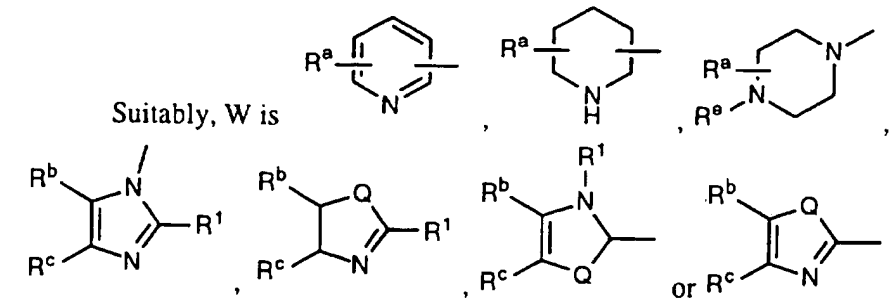
t is 0 to 2;

and pharmaceutically acceptable salts thereof.

The compounds of formula (I) inhibit the binding of vitronectin and other RGD-containing peptides to the vitronectin ($\alpha_v\beta_3$) receptor, and of fibrinogen to the fibrinogen (GPIIbIIIa) receptor. Inhibition of the vitronectin receptor on osteoclasts inhibits osteoclastic bone resorption and is useful in the treatment of diseases wherein bone resorption is associated with pathology, such as osteoporosis. Inhibition of the fibrinogen receptor and the vitronectin receptor is useful for inhibiting aggregation of platelets to one another and to vascular surfaces, such as may be found in conditions of undesirable or inappropriate platelet aggregation, or conditions wherein the vascular wall of the endothelium may be damaged, irregular or abnormally adhesive, for instance in states such as restenosis or atherosclerosis.

Suitably, X-X' is NH-CH or CH_2-CH.

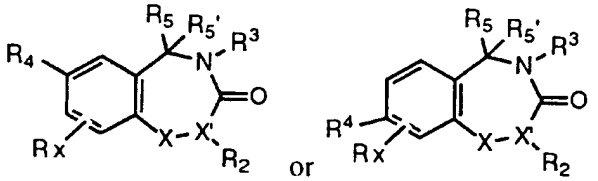
Suitably, Y is  or W-$(CH_2)_q$.

Suitably, W is  where R^a is H, C_{1-4}alkyl, Ar-C_{0-4}alkyl, OH, NO_2, $N(R^1)_2$, $CON(R^1)_2$, $(CH_2)_qN(R^1)_2$, $C(O)N(R^1)_2$, $=N\text{-}OR^1$, $R^1HN\text{-}C(=NH)\text{-}NH$ or $R^1HN\text{-}C(=NH)$, and R^b and R^c are independently selected from H, C_{1-6}alkyl, Ar-C_{0-6}alkyl, Het-C_{0-6}alkyl, C_{3-6}cycloalkyl-C_{0-6}alkyl, halogen, C_{1-6}alkyl, OR^1, SR^1, COR^1, OH, NO_2, $N(R^1)_2$, $CO(NR^1)_2$, $CH_2N(R^1)_2$, or R^b and R^c are joined together to form a five or six membered aromatic or non-aromatic ring, optionally substituted by halogen, C_{1-4}alkyl, OR^1, SR^1, COR^1, OH, NO_2, $N(R^1)_2$, $CO(NR^1)_2$, $CH_2N(R^1)_2$; and R^e is H, C_{1-4}alkyl, Het-C_{0-4}alkyl or Ar-C_{0-4}alkyl;

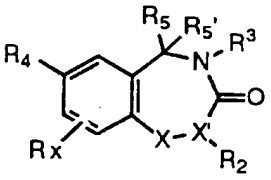
Suitably R^b and R^c are joined together to form an optionally substituted phenyl or pyridyl ring. Suitably, W is imidazolidinyl, imidazolyl or benzimidazolyl. Suitably U is -NH-N=CH-. Preferably q is 0.

Suitably R^e is H, C_{1-6}alkyl. or substituted or unsubstituted phenyl, pyridinyl or piperidinyl. Suitably, when Z is phenyl, or $(CH_2)_t$ with q+r+t being greater than 1, W is $N(R^1)_2\text{-}(CH_2)_q$, $R^1HN\text{-}C(=NH)$, $R^1HN\text{-}C(=NH)\text{-}NH$ or OH.

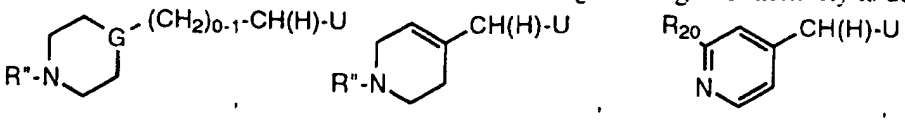
Suitably, when it is desired that compounds of formula (I) should have selective affinity for the fibrinogen receptor, R^4 is preferably substituted as:

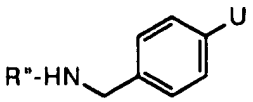
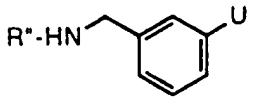


Suitably, when it is desired that compounds of formula (I) should have selective affinity for the vitronectin receptor, R^4 is preferably substituted as:



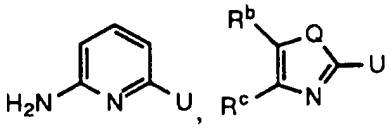
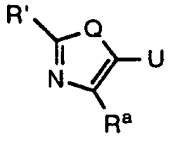
Suitable substituents for R^4 when fibrinogen antagonist acitivity is desired are:



R"HNC(=NH)NH-(CH_2)-CH(H)-U, and R"HN-(CH_2)$_2$-CH(H)-U wherein G is N or CH, R^{20} is hydrogen, amino, mono or di-C_{1-4}alkylamino, hydroxy or C_{1-4}alkyl, and (H) indicates an optional hydrogen depending upon whether U is attached as a single or doubly bonded nitgrogen.

Preferred substituents for R^4 when vitronectin binding activity is desired are:


and

, wherein Q is NH. Particularly preferred are compounds wherein R^b and R^c are joined to form a phenyl or pyridyl ring.

Preferably n is 1.

Preferably R is H.

Preferably R^1 is H or C_{1-4}alkyl.

Preferably R^3 is H, C_{1-4}alkyl or phenylethyl.

Preferably R^5 and $R^{5'}$ are H,H.

Representative of the novel compounds of this invention are the following:

(±)-7-[[2-(Imidazolidinyl)azino]methyl]]-4-methyl-3-oxo-2,3,4,5-tetrahydro-1H-1,4-benzodiazepine-2-acetic acid;

(±)-7-[[2-(Imidazolidinyl)hydrazino]carbonyl]]-4-methyl-3-oxo-2,3,4,5-tetrahydro-1H-1,4-benzodiazepine-2-acetic acid;

(±)-7-[[(2-Benzimidazolyl)azino]methyl]]-4-methyl-3-oxo-2,3,4,5-tetrahydro-1H-2-benzazepine-4-acetic acid; and

(±)-7-[[2-(1-Benzimidazolyl)hydrazino]carbonyl]]-4-methyl-3-oxo-2,3,4,5-tetrahydro-1H-1,4-benzodiazepine-2-acetic acid.

In cases wherein the compounds of this invention may have one or more chiral centers, unless specified, this invention includes each unique nonracemic compound which may be synthesized and resolved by conventional techniques. In cases in which compounds have unsaturated carbon-carbon double bonds, both the cis (Z) and trans (E) isomers are within the scope of this invention. In cases wherein compounds may exist in tautomeric forms, for instance, keto-enol tautomers and enamine tautomers of the hydrazino linkage, each tautomeric form is contemplated as being included within this invention whether existing in equilibrium or thermodynamically or chemically locked in

one form. It will be appreciated that when U is =N-N=CH, it will not be directly attached to an aromatic ring. The meaning of any substituent at any one occurrence is independent of its meaning, or any other substituent's meaning, at any other occurrence, unless specified otherwise.

C_{1-4}alkyl as applied herein means an optionally substituted alkyl group of 1 to 4 carbon atoms, and includes methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl and t-butyl. C_{1-6}alkyl additionally includes pentyl, n-pentyl, isopentyl, neopentyl and hexyl and the simple aliphatic isomers thereof. C_{0-4}alkyl and C_{0-6}alkyl additionally indicates that no alkyl group need be present (*e.g.*, that a covalent bond is present).

A substituent on a C_{1-6} alkyl group, may be on any carbon atom which results in a stable structure, and is available by conventional synthetic techniques. Suitable substituents are those which comprise R^x, such as C_{1-4}alkyl, OR^1, SR^1, C_{1-4}alkyl, C_{1-4}alkylsulfonyl, C_{1-4}alkylsulfoxyl, -CN, $N(R^1)_2$, $CH_2N(R^1)_2$, $-NO_2$, $-CF_3$, $-CO_2R^3$ $-CON(R^1)_2$, $-COR^1$, $-NR^1C(O)R^1$, OH, F, Cl, Br, I, or $CF_3S(O)_r$-,wherein r is 0 to 2.

Ar, or aryl, as applied herein, means phenyl or naphthyl, or phenyl or naphthyl substituted by one to three substituents, such as those defined above for alkyl, especially C_{1-4}alkyl, C_{1-4}alkoxy, C_{1-4}alkylthio, trifluoroalkyl, OH, F, Cl, Br or I.

Het, or heterocycle, indicates an optionally substituted five or six membered monocyclic ring, or a nine or ten-membered bicyclic ring containing one to three heteroatoms chosen from the group of nitrogen, oxygen and sulfur, which are stable and available by conventional chemical synthesis. Illustrative heterocycles are benzofuryl, benzimidazole, benzopyran, benzothiophene, furan, imidazole, indoline, morpholine, piperidine, piperazine, pyrrole, pyrrolidine, tetrahydropyridine, pyridine, thiazole, thiophene, quinoline, isoquinoline, and tetra- and perhydro- quinoline and isoquinoline. Any accessible combination of up to three substituents on the Het ring, such as those defined above for alkyl that are available by chemical synthesis and are stable are within the scope of this invention.

C_{3-7}cycloalkyl refers to an optionally substituted carbocyclic system of three to seven carbon atoms, which may contain up to two unsaturated carbon-carbon bonds. Typical of C_{3-7}cycloalkyl are cyclopropyl, cyclobutyl, cyclopentyl, cyclopentenyl, cyclohexyl, cyclohexenyl and cycloheptyl. Any combination of up to three substituents, such as those defined above for alkyl, on the cycloalkyl ring that is available by conventional chemical synthesis and is stable, is within the scope of this invention.

(N) as used herein indicates a nitrogen heterocycle, which may be a saturated or unsaturated stable five-, six- or seven-membered monocyclic ring, or a seven- to ten-membered bicyclic ring containing up to three nitrogen atoms or containing one nitrogen

atom and a heteroatom chosen from oxygen and sulfur, and which may be substituted on any atom that results in a stable structure. The nitrogen atom in such ring may be substituted so as to result in a quaternary nitrogen. The nitrogen heterocycle may be substituted in any stable position by, for instance H, C_{1-4}alkyl, C_{1-4}alkoxy, F, Cl, Br, I, NO_2, $N(R^1)_2$, OH, CO_2R^1, $CONHR^1$, CF_3, Ar-C_{0-4}alkyl, Ar-C_{0-4}alkyl-$S(O)_r$ (*e.g.*, where r is 0, 1 or 2) or C_{1-4}alkyl substituted by any of the aforementioned substituents.

Representative of (N) are pyrroline, pyrrolidine, imidazole, imidazoline, imidazolidine, benzimidazole, benzothiazole, benzoxazole, oxazole, thiazole, indane, indole, pyrazole, pyrazoline, pyrazolidine, piperidine, piperazine, morpholine, pyridine, pyridinium, tetrahydropyridine, tetrahydro- and hexahydro-azepine, quinuclidine, quinuclidinium, quinoline, isoquinoline, and tetra- and perhydro- quinoline and isoquinoline. In particular, (N) may be imidazolidinyl, imidazolyl, benzimidazolyl, pyridyl, pyrolidinyl, piperidinyl, piperazinyl, azetidinyl, quinuclidinyl or tetrahydropyridinyl. (N) is preferably 2-imidazolyl, 2-benzimidazolyl, 4-pyridyl, 4-(2-amino-pyridyl), 4-tetrahydropyridyl, 4-piperidinyl or 4-piperazinyl.

When R^b and R^c are joined together to form a five- or six-membered aromatic or non-aromatic ring fused to the ring to which R^b and R^c are attached, the ring formed will generally be a five- or six-membered heterocycle selected from those listed above for Het, especially pyridine, or will be a phenyl, cyclohexyl or cyclopentyl ring.

Benzimidazolyl, 4-azabenzimidazolyl, 5-azabenzimidazolyl and substituted derivatives thereof are preferred moieties for W when vitronectin receptor antagonist activity is desired.

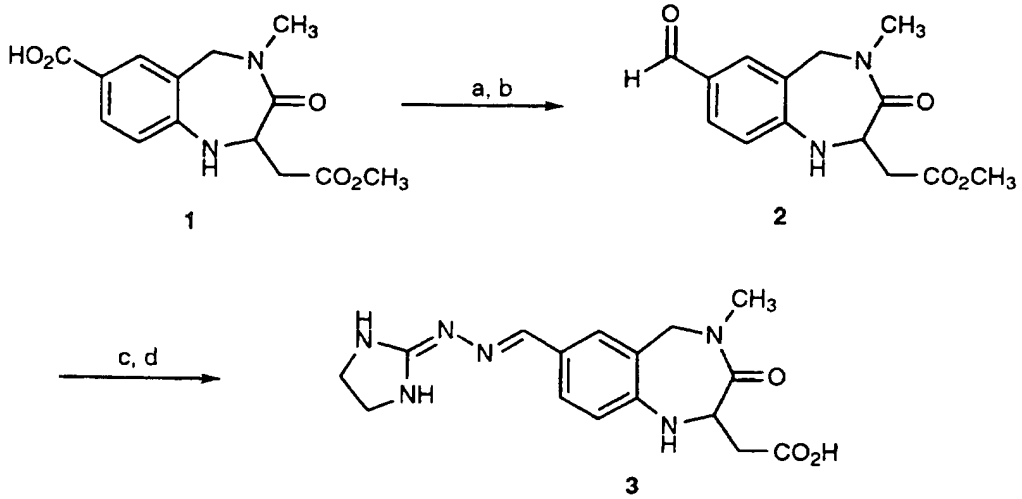
A methyl, ethyl, t-Bu, cHex, benzyl, substituted benzyl, (pivaloyl)methyl or (2-methyl-2-methoxypropanoyl)methyl ester may be used for the protection of the carboxyl group. Suitable substitution of the benzyl protecting groups is ortho and/or para substitution with chloro, bromo, nitro, methoxy or methyl.

Certain radical groups are abbreviated herein. t-Bu refers to the tertiary butyl radical, Boc refers to the t-butyloxycarbonyl radical, Fmoc refers to the fluorenylmethoxycarbonyl radical, Ph refers to the phenyl radical, Cbz refers to the benzyloxycarbonyl radical, BrZ refers to the o-bromobenzyloxycarbonyl radical, ClZ refers to the o-chlorobenzyloxycarbonyl radical, Bzl refers to the benzyl radical, 4-MBzl refers to the 4-methyl benzyl radical, Me refers to methyl, Et refers to ethyl, Ac refers to acetyl, Alk refers to C_{1-4}alkyl, Nph refers to 1- or 2-naphthyl and cHex refers to cyclohexyl.

Certain reagents are abbreviated herein. DCC refers to dicyclohexylcarbodiimide. DMAP refers to dimethylaminopyridine, DIEA refers to diisopropylethyl amine, EDC refers to N-ethyl-N'(dimethylaminopropyl)-carbodiimide. HOBt refers to 1-hydroxybenzotriazole, THF refers to tetrahydrofuran, DIEA refers to diisopropylethylamine, DMF refers to dimethyl formamide, NBS refers to N-bromo-succinimide, Pd/C refers to a palladium on carbon catalyst, PPA refers to 1-propanephosphonic acid cyclic anhydride, DPPA refers to diphenylphosphoryl azide, BOP refers to benzotriazol-1-yloxy-tris(dimethylamino)phosphonium hexafluorophosphate, HF refers to hydrofluoric acid, TEA refers to triethylamine, TFA refers to trifluoroacetic acid, PCC refers to pyridinium chlorochromate.

The preparation of compounds of formula I, wherein U is a hydrazone, is illustrated by the method described in Scheme 1 by condensation of an aldehyde with an appropriate substituted hydrazine.

Scheme 1



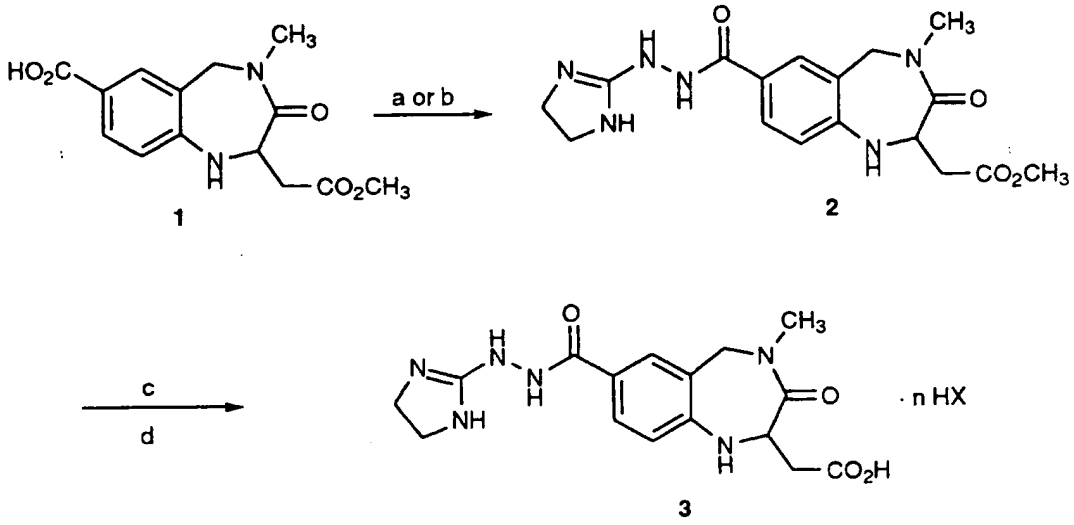
a) $SOCl_2$, reflux; b) H_2, 10% Pd/C, THF, 2,6-lutidine ; c) hydrazinoimidazolidine, EtOH, reflux; d) 1.0 N NaOH, MeOH; e) acidification.

In Scheme 1, methyl (±)-7-carboxy-4-methyl-3-oxo-2,3,4,5-tetrahydro-1H-1,4-benzodiazepine-2-acetate (1-Scheme 1), prepared as described by Bondinell, et al. (WO 93/00095), is converted to the corresponding acid chloride in refluxing $SOCl_2$, and is subsequently reduced with an appropriate reducing agents or hydrogen in the presence of catalyst such Pd/C to afford the corresponding aldehyde, 2-Scheme 1. The aldehyde is condensed with hydrazine derivatives in refluxing methanol to give substituted azino methyl ester intermediate. The substituted azino methyl ester intermediate is hydrolysed

in aqueous NaOH in methanol to afford the intermediate carboxylate salt which is acidified with a suitable acid, for instance, acetic acid, TFA or HCl, to afford the carboxylic acid 3-Scheme 1. Alternatively, the intermediate carboxylate salt can be isolated, if desired.

The preparation of compounds, wherein U is an acyl hydrazide, is illustrated by Scheme 2.

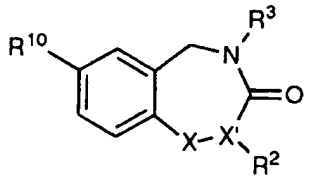
Scheme 2



a) EDC, HOBT, $(i\text{-}Pr)_2NEt$, DMF, hydrazinoimidazole; b) $SOCl_2$, reflux; 2-hydrazinoimidazoline, pyridine, CH_2Cl_2; c) 1.0 N NaOH, aqueous THF or MeOH; d) acidification.

In Scheme 2, methyl (±)-7-carboxy-4-methyl-3-oxo-2,3,4,5-tetrahydro-1H-1,4-benzodiazepine-2-acetate (1-Scheme 2) is converted to an activated form of the carboxylic acid using, for example, EDC and HOBT or $SOCl_2$, and the activated form is subsequently reacted with an appropriate hydrazine to afford the corresponding hydrazide 2-Scheme 2. Many additional methods for converting a carboxylic acid to a hydrazide are known, and can be found in standard reference books, such as "Compendium of Organic Synthetic Methods", Vol. I - VI (published by Wiley-Interscience). The methyl ester of 2-Scheme 2 is hydrolyzed using aqueous base, for example, aqueous LiOH in THF or aqueous NaOH in methanol, and the intermediate carboxylate salt is acidified with a suitable acid, for instance HOAc, TFA or HCl, to afford the carboxylic acid 3-Scheme 2. Alternatively, the intermediate carboxylate salt can be isolated, if desired.

The core 6-7 bicyclic ring system is prepared from compounds of the general formula (II):

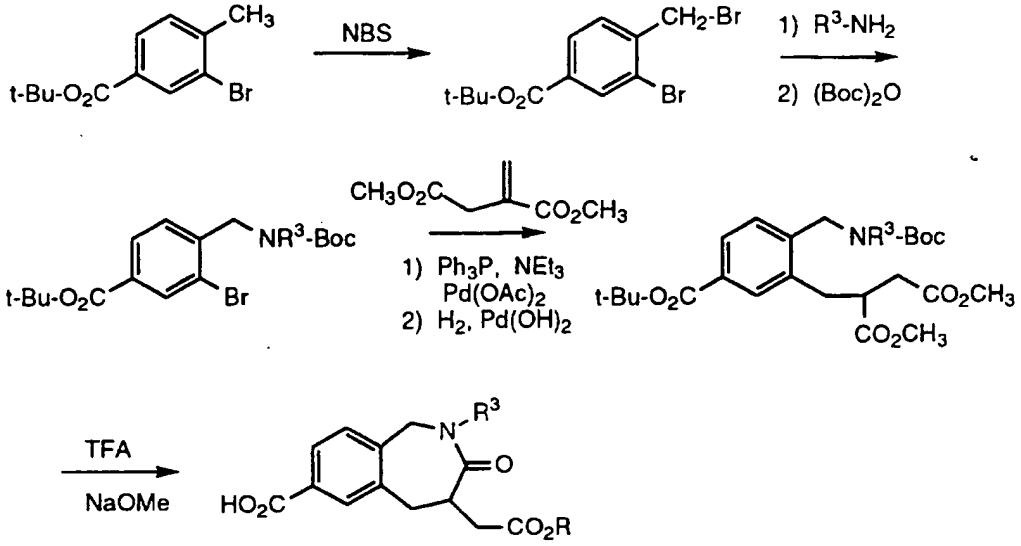


(II)

wherein R^{10} is CO_2H or a synthetic equivalent thereof, X and X' are as defined for formula (I) and R^2 and R^3 are as defined in formula (I) with any reactive groups protected. Representative methods for preparing the substituted benzodiazepine nucleus are well known in the art, *e.g.*, Hynes, *et al.*, *J. Het. Chem.*, 1988, 25, 1173; Muller, *et al.*, *Helv. Chim. Acta.*, 1982, 65, 2118; Mori, *et al.*, *Heterocycles*, 1981, 16, 1491. Similarly, methods for preparing benzazepines, 1,4-benzothiazepines, 1,4-benzoxazepines and 1,4-benzodiazepines are known and are disclosed, for instance, in Bondinell, *et al.*, International Patent Application WO 93/00095.

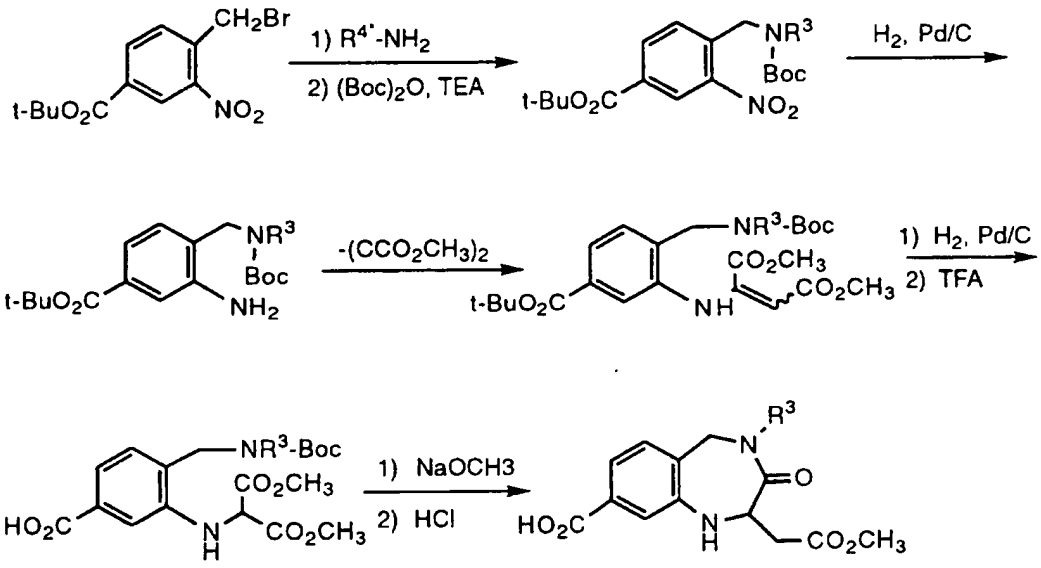
A representative method for preparing the benzazepine nucleus is given by Scheme 3. A representative method for preparing a benzodiazepine nucleus is given by Schemes 4 and 5. Benzoxazepines and benzothiazepines may be prepared using analogous chemistry, except starting, for instance, with t-butyl 3-bromomethyl-4-(4-methoxy)benzyloxy-benzoate or methyl 3-bromomethyl-4-(4-methoxy)benzylthio-benzoate which are converted by routine methods to the corresponding t-butyl 3-(butyloxycarbonyl)aminomethyl-4-hydroxy-benzoate or t-butyl 3-(butyloxycarbonyl)aminomethyl-4-mercapto-benzoate.

Scheme 3

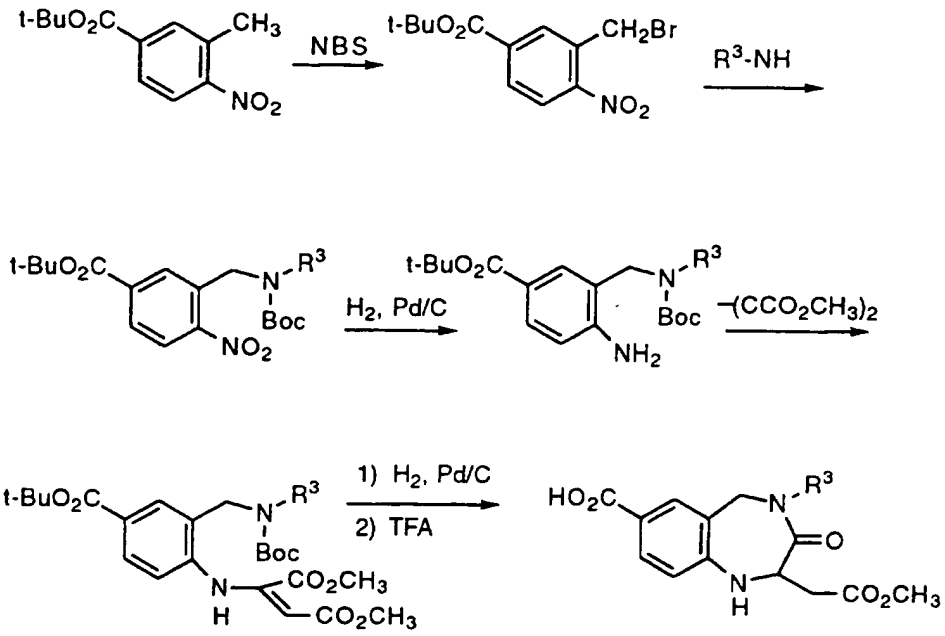


NBS = N-bromosuccinimide

Scheme 4



Scheme 5



The simple tri-substituted benzene starting materials, and the hydrazines are commercially available or are prepared by routine methods well known in the art.

Coupling reagents as used herein denote reagents which may be used to form amide or hydrazide bonds. Typical coupling methods employ carbodiimides, activated anhydrides and esters and acyl halides. Reagents such as EDC, DCC, DPPA, PPA, BOP reagent, HOBt, N-hydroxysuccinimide and oxalyl chloride are typical.

Coupling methods to form amide bonds are generally well known to the art. The methods of peptide synthesis generally set forth by Bodansky *et al.*, THE PRACTICE OF PEPTIDE SYNTHESIS, Springer-Verlag, Berlin, 1984, Ali *et al.* in *J. Med. Chem.*, 29, 984 (1986) and *J. Med. Chem.*, 30, 2291 (1987) are generally illustrative of the technique and are incorporated herein by reference.

Typically, the hydrazine is coupled via a free amino group to an appropriate carboxylic acid substrate using a suitable carbodiimide coupling agent, such as N,N' dicyclohexyl carbodiimide (DCC), optionally in the presence of catalysts such as 1-hydroxybenzotriazole (HOBt) and dimethylamino pyridine (DMAP). Other methods, such as the formation of activated esters, anhydrides or acid halides, of the free carboxyl of a suitably protected acid substrate, and subsequent reaction with the free amine of a suitably protected hydrazine, optionally in the presence of a base, are also suitable. For example, a carboxylic acid is treated with isobutyl chloroformate in a solvent such as methylene chloride or tetrahydrofuran (THF), in the presence of a base, such as N-methyl

morpholine, DMAP or a trialkylamine, to form the "activated anhydride", which is subsequently reacted with the free amine of hydrazine.

Methods to form hydrazones are also well known to the art, and generally proceed by condensing an aldehyde with a hydrazine, optionally in the presence of an acid catalyst or a dehydrating agent.

Acid addition salts of the compounds are prepared in a standard manner in a suitable solvent from the parent compound and an excess of an acid, such as hydrochloric, hydrobromic, hydrofluoric, sulfuric, phosphoric, acetic, trifluoroacetic, maleic, succinic or methanesulfonic. Certain of the compounds form inner salts or zwitterions which may be acceptable. Cationic salts are prepared by treating the parent compound with an excess of an alkaline reagent, such as a hydroxide, carbonate or alkoxide, containing the appropriate cation; or with an appropriate organic amine. Cations such as Li^+, Na^+, K^+, Ca^{++}, Mg^{++} and NH_4^+ are specific examples of cations present in pharmaceutically acceptable salts.

This invention also provides a pharmaceutical composition which comprises a compound according to formula (I) and a pharmaceutically acceptable carrier. Accordingly, the compounds of formula (I) may be used in the manufacture of a medicament. Pharmaceutical compositions of the compounds of formula (I) prepared as hereinbefore described may be formulated as solutions or lyophilized powders for parenteral administration. Powders may be reconstituted by addition of a suitable diluent or other pharmaceutically acceptable carrier prior to use. The liquid formulation may be a buffered, isotonic, aqueous solution. Examples of suitable diluents are normal isotonic saline solution, standard 5% dextrose in water or buffered sodium or ammonium acetate solution. Such formulation is especially suitable for parenteral administration, but may also be used for oral administration or contained in a metered dose inhaler or nebulizer for insufflation. It may be desirable to add excipients such as polyvinylpyrrolidone, gelatin, hydroxy cellulose, acacia, polyethylene glycol, mannitol, sodium chloride or sodium citrate.

Alternately, these compounds may be encapsulated, tableted or prepared in a emulsion or syrup for oral administration. Pharmaceutically acceptable solid or liquid carriers may be added to enhance or stabilize the composition, or to facilitate preparation of the composition. Solid carriers include starch, lactose, calcium sulfate dihydrate, terra alba, magnesium stearate or stearic acid, talc, pectin, acacia, agar or gelatin. Liquid carriers include syrup, peanut oil, olive oil, saline and water. The carrier may also include a sustained release material such as glyceryl monostearate or glyceryl distearate, alone or with a wax. The amount of solid carrier varies but, preferably, will be between about 20 mg to about 1 g per dosage unit. The pharmaceutical preparations are made

following the conventional techniques of pharmacy involving milling, mixing, granulating, and compressing, when necessary, for tablet forms; or milling, mixing and filling for hard gelatin capsule forms. When a liquid carrier is used, the preparation will be in the form of a syrup, elixir, emulsion or an aqueous or non-aqueous suspension. Such a liquid formulation may be administered directly p.o. or filled into a soft gelatin capsule.

For rectal administration, the compounds of this invention may also be combined with excipients such as cocoa butter, glycerin, gelatin or polyethylene glycols and molded into a suppository.

The compounds described herein are antagonists of integrin receptors, particularly the fibrinogen and vitronectin receptor. Fibrinogen receptor antagonists is useful for treating acute myocardial infarction (AMI), deep vein thrombosis, pulmonary embolism, dissecting anurysm, transient ischemia attack (TIA), stroke and other infarct-related disorders, and unstable angina. Chronic or acute states of hyper-aggregability, such as disseminated intravascular coagulation (DIC), septicemia, surgical or infectious shock, post-operative and post-partum trauma, cardiopulmonary bypass surgery, incompatible blood transfusion, abruptio placenta, thrombotic thrombocytopenic purpura (TTP), snake venom and immune diseases, are likely to be responsive to such treatment. In addition, vitronectin receptor antagonists are useful for the treatment of diseases wherein loss of the bone matrix creates pathology. Thus, the compounds are useful for the instant compounds are also useful for the treatment of osteoporosis, hyperparathyroidism, Paget's disease, hypercalcemia of malignancy, osteolytic lesions produced by bone metastasis, bone loss due to immobilization or sex hormone deficiency. The compounds of this invention having significant vitronectin receptor antagonist activity are also believed to have utility as anti-angiogenic, anti-tumor, anti-inflammatory and anti-metastatic agents, and be useful in the treatment of atherosclerosis and restenosis.

The compound is administered either orally or parenterally to the patient, in a manner such that the concentration of drug is sufficient to inhibit bone resorption, or other such indication. The pharmaceutical composition containing the peptide is administered at an oral dose of between about 0.1 to about 50 mg/kg in a manner consistent with the condition of the patient. Preferably the oral dose would be about 0.5 to about 20 mg/kg. For acute therapy, parenteral administration is preferred. An intravenous infusion of the peptide in 5% dextrose in water or normal saline, or a similar formulation with suitable excipients, is most effective, although an intramuscular bolus injection is also useful. Typically, the parenteral dose will be about 0.01 to about 100 mg/kg; preferably between 0.1 and 20 mg/kg. The compounds are administered one to four times daily at a level to achieve a total daily dose of about 0.4 to about 400

mg/kg/day. The precise level and method by which the compounds are administered is readily determined by one routinely skilled in the art by comparing the blood level of the agent to the concentration required to have a therapeutic effect.

The compounds may be tested in one of several biological assays to determine the concentration of compound which is required to have a given pharmacological effect.

Competitive Binding to GPIIb-IIIa

The binding to the fibrinogen receptor (GPIIb-IIIa) was assayed by an indirect competitive binding method using [^{3}H]-SK&F-107260 as an RGD-type ligand. The binding assay was performed in a 96-well filtration plate assembly (Millipore Corporation, Bedford, MA) using 0.22 um hydrophilic durapore membranes. The wells were precoated with 0.2 mL of 10 µg/mL polylysine (Sigma Chemical Co., St. Louis, MO.) at room temperature for 1 h to block nonspecific binding. Various concentrations of unlabeled benzodiazapines were added to the wells in quadruplicate. [^{3}H]-SK&F-107260 was applied to each well at a final concentration of 4.5 nM, followed by the addition of 1 µg of the purified platelet GPIIb-IIIa-containing liposomes. The mixtures were incubated for 1 h at room temperature. The GPIIb-IIIa-bound [3H]-SK&F-107260 was separated from the unbound by filtration using a Millipore filtration manifold, followed by washing with ice-cold buffer (2 times, each 0.2 mL). Bound radioactivity remaining on the filters was counted in 1.5 mL Ready Solve (Beckman Instruments, Fullerton, CA) in a Beckman Liquid Scintillation Counter (Model LS6800), with 40% efficiency. Nonspecific binding was determined in the presence of 2 µM unlabeled SK&F-107260 and was consistently less than 0.14% of the total radioactivity added to the samples. All data points are the mean of quadruplicate determinations.

Competition binding data were analyzed by a nonlinear least-squares curve fitting procedure. This method provides the IC50 of the antagonists (concentration of the antagonist which inhibits specific binding of [^{3}H]-SK&F-107260 by 50% at equilibrium). The IC50 is related to the equilibrium dissociation constant (Ki) of the antagonist based on the Cheng and Prusoff equation: $Ki = IC50/(1+L/Kd)$, where L is the concentration of [3H]-SK&F-107260 used in the competitive binding assay (4.5 nM), and Kd is the dissociation constant of [3H]-SK&F-107260 which is 4.5 nM as determined by Scatchard analysis.

Inhibition of Platelet Aggregation

Blood was collected (citrated to prevent coagulation) from, naive, adult mongrel dogs. Platelet rich plasma, PRP, was prepared by centrifugation at 150 x g for 10 min at room temperature. Washed platelets were prepared by centrifuging PRP at 800 x g for 10

min. The cell pellet thus obtained was washed twice in Tyrode's buffer (pH 6.5) without Ca^{++} and resuspended in Tyrode's buffer (pH 7.4) containing 1.8 mM Ca^{++} at 3 x 10^5 cells/ml. Peptides were added 3 min prior to the agonist in all assays of platelet aggregation. Final agonist concentrations were 0.1 unit/ml thrombin and 2 mM ADP (Sigma). Aggregation was monitored in a Chrono-Log Lumi-Aggregometer. Light transmittance 5 min after addition of the agonist was used to calculate percent aggregation according to the formula % aggregation = [(90-CR) + (90-10)] x 100, where CR is the chart reading, 90 is the baseline, and 10 is the PRP blank reading. IC50's were determined by plotting [% inhibition of aggregation] vs. [concentration of peptide]. Peptides were assayed at 200 mM and diluted sequentially by a factor of 2 to establish a suitable dose response curve.

The compounds of this invention inhibit the aggregation of human platelets stimulated with ADP with IC50 of about 0.02 to about 200 μM. Preferred compounds have IC50 of less than 1 μM. The most preferred compounds have IC50 of less than 0.1 μM.

Inhibition of vitronectin binding

Solid-Phase [^{3}H]-SK&F-107260 Binding to $\alpha_v\beta_3$: Human placenta or human platelet $\alpha_v\beta_3$ (0.1-0.3 mg/mL) in buffer T (containing 2 mM $CaCl_2$ and 1% octylglucoside) was diluted with buffer T containing 1 mM $CaCl_2$, 1 mM $MnCl_2$, 1 mM $MgCl_2$ (buffer A) and 0.05% NaN_3, and then immediately added to 96-well ELISA plates (Corning, New York, NY) at 0.1 mL per well. 0.1 - 0.2 μg of $\alpha_v\beta_3$ was added per well. The plates were incubated overnight at 4°C. At the time of the experiment, the wells were washed once with buffer A and were incubated with 0.1 mL of 3.5% bovine serum albumin in the same buffer for 1 hr at room temperature. Following incubation the wells were aspirated completely and washed twice with 0.2 mL buffer A.

Compounds were dissolved in 100% DMSO to give a 2 mM stock solution, which was diluted with binding buffer (15 mM Tris-HCl (pH 7.4), 100 mM NaCl, 1 mM $CaCl_2$, 1 mM $MnCl_2$, 1 mM $MgCl_2$) to a final compound concentration of 100 μM. This solution is then diluted to the required final compound concentration. Various concentrations of unlabeled antagonists (0.001 - 100 μM) were added to the wells in triplicates, followed by the addition of 5.0 nM of [^{3}H]-SK&F-107260 (65 - 86 Ci/mmol).

The plates were incubated for 1 hr at room temperature. Following incubation the wells were aspirated completely and washed once with 0.2 mL of ice cold buffer A in a well-to-well fashion. The receptors were solubilized with 0.1 mL of 1% SDS and the bound [^{3}H]-SK&F-107260 was determined by liquid scintillation counting with the addition of 3 mL Ready Safe in a Beckman LS Liquid Scintillation Counter, with 40%

efficiency. Nonspecific binding of [^{3}H]-SK&F-107260 was determined in the presence of 2 μM SK&F-107260 and was consistently less than 1% of total radioligand input. The IC_{50} (concentration of the antagonist to inhibit 50% binding of [^{3}H]-SK&F-107260) was determined by a nonlinear, least squares curve-fitting routine, which was modified from the LUNDON-2 program. The K_i (dissociation constant of the antagonist) was calculated according to the equation: $K_i = IC_{50}/(1 + L/K_d)$, where L and K_d were the concentration and the dissociation constant of [^{3}H]-SK&F-107260, respectively.

Compounds of this invention may also be tested for *in vitro* and *in vivo* bone resorption in assays standard in the art for evaluating inhibition of bone formation, such as the pit formation assay disclosed in EP 528 587, which may also be performed using human osteoclasts in place of rat osteoclasts, and the ovarectomized rat model, described by Wronski *et al., Cells and Materials* 1991, Sup. 1, 69-74.

The compound of Example 1 inhibited binding to the vitronectin receptor at a concentration of 1.4 uM, and inhibited platelet aggregation at a concentration of 2.4 uM.

Examples

Nuclear magnetic resonance spectra were recorded at either 250 or 400 MHz using, respectively, a Bruker AM 250 or Bruker AC 400 spectrometer. $CDCl_3$ is deuteriochloroform, DMSO-d_6 is hexadeuteriodimethylsulfoxide, and CD_3OD is tetradeuteriomethanol. Chemical shifts are reported in parts per million (δ) downfield from the internal standard tetramethylsilane. Abbreviations for NMR data are as follows: s=singlet, d=doublet, t=triplet, q=quartet, m=multiplet, dd=doublet of doublets, dt=doublet of triplets, app=apparent, br=broad. J indicates the NMR coupling constant measured in Hertz. Infrared (IR) spectra were recorded on a Perkin-Elmer 683 infrared spectrometer in transmission mode. IR band positions are reported in inverse wavenumbers (cm^{-1}). Mass spectra were taken on either VG 70 FE, PE Syx API III, or VG ZAB HF instruments, using fast atom bombardment (FAB) or electrospray (ES) ionization techniques. Elemental analyses were obtained using a Perkin-Elmer 240C elemental analyzer. Melting points were taken on a Thomas-Hoover melting point apparatus and are uncorrected. All temperatures are reported in degrees Celsius.

Methyl (±)-7-carboxy-3-oxo-2-(2-phenylethyl)-2,3,4,5-tetrahydro-1H-1,4-benzodiazepine-2-acetate, methyl (±)-7-carboxy-4-methyl-3-oxo-2,3,4,5-tetrahydro-1H-1,4-benzodiazepine-2-acetate was prepared by the method of Bondinell, et al., WO 93/00095.

Example 1

Preparation of (+/-)-2,3,4,5-tetrahydro-7-[[2-imidazolidinyl)azino]methyl]-4-methyl-3-oxo-1H-1,4-benzodiazepine-2-acetic acid

a) Methyl (+/-)-7-(formyl)-2,3,4,5-tetrahydro-4-methyl-3-oxo-1H-1,4-benzodiazepine-2-acetate

A mixture of methyl (±)-7-carboxy-4-methyl-3-oxo-2,3,4,5-tetrahydro-1H-1,4-benzodiazepine-2-acetate (1.4 g, 4.5 mmol) and thionyl chloride (30 mL) was refluxed for 1 hr. The resulting orange solution was concentrated to dryness to a foam. This was suspended in THF (30 ml), 2,6-lutidine (0.53 mL, 4.5 mmol) was added and the mixture was purged with argon. 10% Pd/C (280 mg) was added and mixture was flushed with hydrogen and maintained under a hydrogen balloon for 20 h. The catalyst was filtered and washed with CH_2Cl_2 (10 mL). The filtrate was concentrated and reconstituted in EtOAc. The organic layer was washed sequentially with 10% NH_4Cl solution and brine, dried over $MgSO_4$, filtered and evaporated to yield the titled compound (600 mg, 48%).

b) methyl (+/-)-2,3,4,5-tetrahydro-7-[[2-imidazolidinyl)azino]methyl}-4-methyl-3-oxo-1H-1,4-benzodiazepine-2-acetate

The compound of Example 1(a) (250 mg, 0.9 mmol) was dissolved in EtOH (25 mL) and the 2-hydrazino-2-imidazole hydrobromide (328 mg, 1.8 mmol) was added. The mixture was brought to reflux for 4 h, then concentrated to dryness, resuspended and triturated with EtOH. The mixture was filtered to yield the title compound as yellow solid (140 mg, 36%).

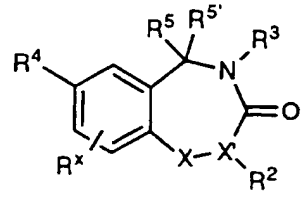
c) (+/-)-2,3,4,5-tetrahydro-7-[[2-(imidazolidinyl)azino]methyl]-4-methyl-3-oxo-1H-1,4-benzodiazepine-2-acetic acid

1 N NaOH (0.65 mL, 0.65 mmole) was added to a cold solution of compound of Example 1(b) (140 mg, 0.32 mmol), MeOH (1.25 mL) and H_2O (0.65 mL). The solution was stirred at room temperature for 3 h. The solvents were evaporated, and the solid was resuspended in 2 mL H_2O and acidified with 1N HOAc. The solid was filtered to yield the title compound (70 mg, 63%). ^1H NMR (400 MHz, DMSO-d_6) δ 2.46 (dd, J=17, 5Hz, 1H), 2.73 (dd, J=17, 9Hz, 1H), 2.96 (s, 3H), 3.49 (s, 4H), 3.79 (d, J=17.1Hz, 1H), 5.05 (m, 1H), 5.52 (d, J=16.1Hz, 1H), 6.57 (d, J= 8.2Hz, 1H), 7.10 (bm, 1H), 7.32 (s. 1H), 7.73 (dd, J= 8.1Hz, 1H), 7.84 (s, 1H), MS (ES) m/e MH+ 345.2, ($M-H^-$) 343.0. Anal. Calcd. for $C_{16}H_{20}N_6O_3$. 0.4HOAc 0.3HBr: C, 51.39; H, 5.62, N, 21.40 Found: C, 51.35; H, 5.98: N, 21.08.

The above description discloses how to make and use the present invention. However, the present invention is not limited to the particular embodiments described hereinabove, but includes all modifications thereof within the scope of the following claims. The various references to journals, patents and other publications which are cited herein are illustrative of the state of the art and are incorporated herein by reference as though fully set forth.

What is claimed is:

1. A compound according to formula (I):



(I)

wherein

X-X' is NR^1-CH, $NC(O)R^3$-CH, N=C, CR^1=C, CHR^1-CH, O-CH or S-CH;

R^1 is H, C_{1-6} alkyl , C_{3-7}cycloalkyl-C_{0-6}alkyl or ArC_{0-6}alkyl;

R^2 is $(CH_2)_nCO_2R$;

R^3 is H, C_{1-6}alkyl, Ar-C_{0-6}alkyl, Het-C_{0-6}alkyl, or C_{3-6}cycloalkyl-C_{0-6}alkyl;

R^4 is Y-U;

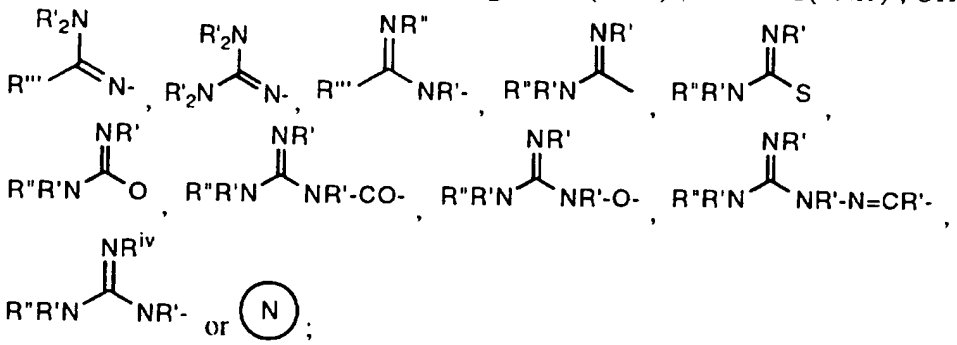
R^5 and $R^{5'}$ are R' or together are =O;

R is H, C_{1-6}alkyl, benzyl or a carboxy protecting group;

U is $-NR^1NR^1C(O)$, =N-N=CH or $-R^1NN$=CH;

Y is W-$(CR'_2)_q$-Z-$(CR'R')_r$-;

W is R'R'"N-, R'R"NR'N-, R'R"NR'NCO-, $R'_2NR'NC(=NR')$-, R'ONR'C(=NR')-, OH,



R' is H, C_{1-6}alkyl, C_{3-7}cycloalkyl-C_{0-4}alkyl or Ar-C_{0-4}alkyl;

R" is R', -COR', CO_2C_{1-6}alkyl or CO_2C_{0-4}alkyl-Ar;

R'" is R', $-CF_3$, -SR', or -OR';

R^{iv} is R', COR', CN, NO_2, SO_2R', CO_2C_{1-6}alkyl or CO_2C_{0-4}alkyl-Ar;

Z is $(CH_2)_t$, Het, Ar or C_{3-7}cycloalkyl;

R^x is H, C_{1-4}alkyl, OR^1, SR^1, C_{1-4}alkyl, C_{1-4}alkylsulfonyl, C_{1-4}alkylsulfoxyl, -CN, $N(R^1)_2$, $CH_2N(R^1)_2$, $-NO_2$, $-CF_3$, $-CO_2R^3$, $-CON(R^1)_2$, $-COR^1$, $-NR^1C(O)R^1$, OH, F, Cl, Br, I, or $CF_3S(O)_r$-;

Q is NR^1, S or O;

n is 0, 1 or 2;

q is 0 to 3;

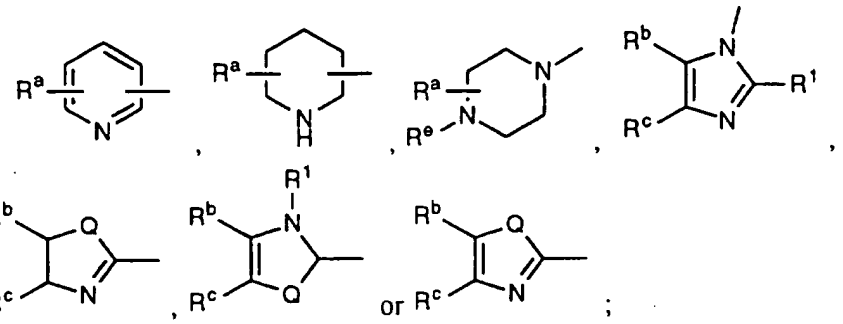
r is 0 to 2;

t is 0 to 2;

and pharmaceutically acceptable salts thereof.

2. A compound according to claim 1 wherein:

Y is W-$(CH_2)_q$;

W is  ;

R^a is H, C_{1-4}alkyl, Ar-C_{0-4}alkyl, OH, NO_2, $N(R^1)_2$, $CON(R^1)_2$, $(CH_2)_qN(R^1)_2$, $C(O)N(R^1)_2$, =N-OR^1, R^1HN-C(=NH)-NH or R^1HN-C(=NH);

R^b and R^c are independently selected from H, C_{1-6}alkyl, Ar-C_{0-6}alkyl, Het-C_{0-6}alkyl, C_{3-6}cycloalkyl-C_{0-6}alkyl, halogen, C_{1-6}alkyl, OR^1, SR^1, COR^1, OH, NO_2, $N(R^1)_2$, $CO(NR^1)_2$, $CH_2N(R^1)_2$, or R^b and R^c are joined together to form a five or six membered aromatic or non-aromatic ring, optionally substituted by halogen, C_{1-4}alkyl, OR^1, SR^1, COR^1, OH, NO_2, $N(R^1)_2$, $CO(NR^1)_2$, $CH_2N(R^1)_2$; and

R^c is H, C_{1-4}alkyl, Het-C_{0-4}alkyl or Ar-C_{0-4}alkyl;

3. A compound according to claim 1 wherein X-X' is NH-CH or CH_2-CH.

4. A compound according to claim 2 wherein W is imidazolyl or benzimidazolyl, and U is NHN=CH-.

5. A compound according to claim 1 selected from the group of:

(±)-7-[[2-(Imidazolidinyl)azino]methyl]]-4-methyl-3-oxo-2,3,4,5-tetrahydro-1H-1,4-benzodiazepine-2-acetic acid;

(±)-7-[[2-(Imidazolidinyl)hydrazino]carbonyl]]-4-methyl-3-oxo-2,3,4,5-tetrahydro-1H-1,4-benzodiazepine-2-acetic acid

(±)-7-[[(2-Benzimidazolyl)azino]methyl]]-4-methyl-3-oxo-2,3,4,5-tetrahydro-1H-2-benzazepine-4-acetic acid; and

(±)-7-[[2-(1-Benzimidazolyl)hydrazino]carbonyl]]-4-methyl-3-oxo-2,3,4,5-tetrahydro-1H-1,4-benzodiazepine-2-acetic acid.

6. A pharmaceutical composition comprising a compound according to claim 1 and a pharmaceutically acceptable carrier.

7. A method of inhibiting a vitronectin receptor comprising administering a compound according to claim 1.

8. A method of inhibiting the fibrinogen receptor comprising administering a compound according to claim 1.

9. A method of inhibiting bone resorption in a mammal comprising administering a compound according to claim 1 and a pharmaceutically acceptable carrier.

10. A method of inhibiting platelet aggregation in a mammal comprising administering a compound according to claim 1 and a pharmaceutically acceptable carrier.

11. The use of a compound according to claim 1 in the manufacture of a medicament.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US96/02483

A. CLASSIFICATION OF SUBJECT MATTER

IPC(6) :C07D 243/24; A61K 31/395
US CL :514/221; 540/504, 512
According to International Patent Clas..ification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

U.S. : 514/221; 540/504, 512

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

CHEMICAL ABSTRACTS DATA BASE IN STN-ON-LINE COMPUTER SYSTEM BASED ON CHEMICAL STRUCTURE.

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y, P	Chem. Abstr., Vol. 123, 28 August 1995 (Columbus, OH, USA), page 1120, column 1, the abstract No. 112082T. Bondinell, W.E. et al., 'Preparation of arylbenzodiazepine derivatives and analogs as fibrinogen antagonists' PCT Int. Appl. WO 94/14,776, 07 July 1994, see entire abstract.	1-4 (in part) and 5-10
Y	Chem. Abstr., Vol. 119, 02 August 1993 (Columbus, OH, USA), page 952, column 1, the abstract No. 49416e, Bondinell, W.E. et al., 'Preparation of 2h-1,4-benzodiazepines as fibrogen antagonists' PCT Int. Appl. WO 93/00,095 07 July 1993, see entire abstract.	1-4 (in part) and 5-10

☐ Further documents are listed in the continuation of Box C. ☐ See patent family annex.

*	Special categories of cited documents:	"T"	later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"A"	document defining the general state of the art which is not considered to be of particular relevance	"X"	document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"E"	earlier document published on or after the international filing date	"Y"	document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"L"	document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)	"&"	document member of the same patent family
"O"	document referring to an oral disclosure, use, exhibition or other means		
"P"	document published prior to the international filing date but later than the priority date claimed		

Date of the actual completion of the international search	Date of mailing of the international search report
06 MAY 1996	28 JUN 1996
Name and mailing address of the ISA/US Commissioner of Patents and Trademarks Box PCT Washington, D.C. 20231 Facsimile No. (703) 305-3230	Authorized officer JOHN M. FORD jd Telephone No. (703) 308-1235

Form PCT/ISA/210 (second sheet)(July 1992)*

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US96/02483

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This international report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

2. ☒ Claims Nos.: 11
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

No description of the "manufacture" or the 'medicament" was given. The process was not clearly set forth to an end.

3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

Please See Extra Sheet.

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☒ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:
1-4 (in part) and 5-10

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest.

☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US96/02483

BOX II. OBSERVATIONS WHERE UNITY OF INVENTION WAS LACKING
This ISA found multiple inventions as follows:

Group I. Claims 1-4 (in part) and 5-10 (in part), where -X-X'- is NR1-CH, NC(O)R3-CH, N=C. These are benzo diazepines in Class 540/subclass 504+ depending on substitution (multiple subclasses).

Group II. Claims 1-10 (in part), where -X-X'- is CR1=C, CHR1-CH, these are benzazepines in Class 540/subclass 569+ depending on specific substitution (multiple subclasses).

Group III. Claims 1, 2, and 4-10 (in part), where -XX'- is O-CH or S-CH; the contain a chalogen (the O or S) in the ring, and the classified in Class 540/subclass 490.

These distinct inventions have acquired separate status in the art, will support patents, and will require different fields of search for the respective inventions. Accordingly, a finding of a lack of unity of invention, as indicated, is considered proper; PCT Article 13.1-13.3.

There is no central core until Applicants pick a -X-X'- value. There is no central special technical feature until applicants pick a -X-X'- value.

The determination of lack of unity of invention is made without regard to whether the three inventions noted are in one claim or more than one claim; PCT Article 13.3.